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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/067,125	02/04/2002	Brenda F. Baker	ISPH-0628	7371

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EXAMINER	
SCHULTZ, JAMES	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 01/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,125	BAKER ET AL.	
	Examiner	Art Unit	
	J. D. Schultz, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *14-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/4/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-13 as they are drawn to Traf-2 in the reply filed on 3 November 2004, is acknowledged. The traversal is on the ground(s) that no additional search burden is put upon the examiner to search the inventions of Groups I, II and III in the same application, because the different inventions are all drawn to oligos that inhibit the expression of Traf or methods of their use, and that a search for one Group would reveal art against another. This is not found persuasive because the inventions are drawn to antisense oligos targeting separate sequences or their methods of use. As set forth by Taylor et al., one particularly useful feature of antisense oligos is the sequence specificity they exhibit for their target transcript. For example, antisense oligos are capable of distinguishing between alternatively spliced variants, or other very closely related sequences, Thus, even though the target sequence of Traf-2 may be related in some way to the target sequence of Traf-6, the sequences are nevertheless different, and accordingly, so are the sequences of the antisense oligos that cause their inhibition. For example, at page 55, lines 27 and 28, it is disclosed that at least one oligo that inhibits Traf-6 does not inhibit Traf-2. Thus, the sequence search for prior art against one gene transcript, Traf-2 for example (the elected sequence), is not coextensive with the search for another. Given the sizes of the oligonucleotide sequence databases, and the fact that Traf-2 and Traf-6 are different sequences, a search and examination of two distinct sequences in the same application is considered to present a serious burden.

Furthermore, the methods of using these oligos, which are claimed presently to include treatments of disease, are also a burden to search in the same application, since the compounds

can be used for methods that are different from treatment. For example, the antisense compounds embrace probes and primers for methods of making or detecting Traf-2 or Traf-6, and thus disclosures describing these probe/primer antisense compounds are not likely to also disclose methods of using antisense inhibitors to treat disease. Accordingly, the searches are divergent and not co-extensive, and are thus a burden to search in the same application.

However, as noted in the restriction requirement mailed 6 October 2004, all Groups set forth therein are linked by claim 1. The restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s), claim 1. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application.

Finally, regarding rejoinder of compounds with their methods of making and using, applicants' attention is directed to the following recitation from paragraph five, "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. §103(b)" (1184 TMOG 86(March 26, 1996)):

> "However, in the case of an elected product claim, rejoinder will be permitted when a product claim is found allowable and the withdrawn process claim **depends from or otherwise includes all the limitations of** an allowed product claim. Withdrawn process claims not commensurate in scope with an allowed product claim will not be rejoined." (emphasis added)

In accordance with M.P.E.P. §821.04 and In re Ochiai, 71 F.3d 1565, 37 USPQ 1127 (Fed. Cir. 1995), rejoinder of product claims with process claims commensurate in scope with the allowed product claims will occur following a finding that the product claims are allowable. Until, such time, a restriction between product claims and process claims is deemed proper. Additionally, in order to retain the right to rejoinder in accordance with the above policy,

Applicant is advised that the process claims should be amended during prosecution to maintain either dependency on the product claims or to otherwise include the limitations of the product claims. Failure to do so may result in a loss of the right to rejoinder.

The requirement is still deemed proper and is therefore made FINAL.

Claims 14-17, and the subject matter of claim 10 drawn to Traf-6, are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3 November 2004.

Priority

Applicants have claimed benefit under 35 U.S.C. 120 to U.S. Application Number 09/167,109, and have included the relationship (i.e., a continuation) to the instant application. However, the status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. Since the parent application has become a patent, the expression "now Patent No. 6,399,297 should follow the filing date of the parent application. This can either be done by applicants during prosecution or by the examiner should the instant application become allowable.

Information Disclosure Statement

The information disclosure statement (IDS) submitted 4 February 2002 was filed before the mailing date of the first Official action on the merits enclosed herein. The submission is in

compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner, and a signed copy is enclosed herewith.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The subject matter of the instantly claimed invention is drawn to antisense compounds that specifically hybridize to and inhibit the expression of Traf-2, and to chemical modifications and pharmaceutically acceptable diluents thereof. The claims are also drawn to methods of use of such antisense compounds including methods of treatment of conditions including cancer, autoimmune disorders, and inflammation.

At the outset it is noted that the rejected claims do not recite any sequence identifier relating to Traf-2. This sequence is thus considered to be defined by its function (i.e. the activity of human tumor necrosis factor receptor-associated factor-2, a.k.a Traf-2) rather than by any one specific structure. Accordingly the claim embraces antisense directed to any sequence of any Traf-2, or any such molecule with analogous Traf-2 activity, known or yet to be discovered,

along with any isoform or allele present within this species, or any variant, polymorphic or otherwise, that is within reasonable similarity from these families of proteins that retain Traf-2 activity.

To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Thus, an applicant complies with the written-description requirement by describing the invention, with all its claimed limitations, and by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical, structure/function correlation, methods of making the claimed product, and any combination thereof. The representative sample requirement may be satisfied by supplying structural or functional information, or a combination of both, such that one of skill in the art would be satisfied that applicants were in possession of the genus as claimed. Further, the size of the representative sample required is an inverse function of the unpredictability of the art.

In order to synthesize the antisense compounds claimed that are directed to Traf-2, one of skill would first need the sequence of Traf-2 in order to synthesize said antisense. However, the only Traf-2 sequence taught in the specification is that of SEQ ID NO: 2. The presence of only one sequence of Traf-2 is not considered to meet the requirements for disclosure of a

representative sample of structures that correlate to the genus of any molecule encompassing any Traf-2, such that one of skill would consider applicants to be in possession of said genus.

However, one of skill in the art could not immediately envision the genus of any sequence of Traf-2 from the disclosure of only one such sequence, particularly in the absence of any teaching by way of structure or reference to active domains or regions. The genus is not immediately envisioned because the genus of any Traf-2 sequence is considered to include not only the Traf-2 sequence of SEQ ID NO: 2, but also any such molecule with analogous Traf-2 activity, known or yet to be discovered, along with any isoform or allele present within this species, or any variant, polymorphic or otherwise, that is within reasonable similarity from these families of proteins that retain Traf-2 activity. However, the distinguishing characteristics of the claimed genus are not considered to be described herein, or in the prior art. Thus, because one of skill in the art could not envision any sequence of any Traf-2, one of skill would not be convinced that applicants were in possession of any antisense sequence against Traf-2 sequences that are heretofore undescribed.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 and 103 that form the basis for the rejections under these sections made in this Office action:

> A person shall be entitled to a patent unless –
>
> 102(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.
>
> 103(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill

in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 2, 10, 11, and 13 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hinuma et al. (U. S. Patent Number 6,048,711).

The claims of the above invention are drawn to antisense compounds 8 to 30 nucleotides in length that specifically hybridize with and inhibit the expression of Traf-2, and to compositions comprising such compounds and pharmaceutically acceptable carriers.

SEQ ID NO: 10 of Hinuma possesses 82.1% complementarity to nucleobases 213-240 of SEQ ID NO: 2, which is the disclosed sequence of Traf-2 of the instant application, and is thus considered to specifically hybridize with Traf-2. Although this reference does not specifically teach the function of inhibiting Traf-2 as claimed in the present application, the above-listed compound of the prior art meets all the structural limitations as set forth in the instant claims. Furthermore, this fragment is disclosed by Hinuma as a primer useful in PCR that is carried out in buffers that are also considered to be pharmaceutically acceptable as diluents. Because the sequence and compounds meet all the structural limitations of the instant claims, they are considered to be substantially identical to applicant's claimed compounds, and in the absence of

evidence to the contrary the sequence and compounds of the prior art are thus considered to possess the functional limitations of specifically hybridizing with and inhibiting the expression of Traf-2. Support for this conclusion is drawn from MPEP § 2112:

> Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim **but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection.** "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims. *Emphasis supplied.*

In rejecting the claims of the above under 35 U.S.C. 102 and 103, a prima facie case has been established by the examiner whereby the burden of proof in showing that the claimed compounds are not anticipated by the compound of the prior art as stated lies with the applicant, as per MPEP 2112.01:

> Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433.

Thus, in the absence of evidence to the contrary, the antisense compounds of the above claims of the instant application are considered anticipated and/or obvious as outlined above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of Lee et al. (J. Exp. Med. Oct. 1998., 188(7) 1381-1384) or Kaye et al. (Proc. Natl. Acad. Sci. USA Oct. 1996, 93:11085-90), in view of Rothe et al., (Cell. 1994 Aug 26; 78(4):681-92., "AI"on applicants IDS), Taylor et al. (Drug Disc. Today, 1999. 4(12)562-567), Baracchini *et al.* (U. S. Patent Number 5,801,154) and Bennett (U. S. Patent Number 5,998,148).

The invention of the above claims is drawn to antisense compounds that target Traf-2, or said compounds comprising internucleoside (i.e. phosphorothioate), sugar (i.e. 2'-O-methoxyethyl), nucleobase (i.e. 5-methylcytosine) or chimeras, or compositions comprising said compounds and pharmaceutically acceptable diluents or colloidal dispersion systems thereof, and methods of use.

Both Lee et al. and Kaye et al. teach inhibition of Traf-2 function via the use of dominant negative mutants. Kaye et al. teaches that inhibition of Traf-2 function inhibits the ability of

LMP1 to activate NF-κB activity, which is an essential event in Epstein-Barr pathogenesis. Lee et al. teaches that Traf-2 is a negative regulator of TNF-α induced apoptosis, and suggest that inhibition of Traf-2 may be part of a larger strategy in treating cancer (see final sentence of discussion). Neither Lee et al. nor Kaye et al. teach antisense compounds that target Traf-2, or said compounds comprising internucleoside (i.e. phosphorothioate), sugar (i.e. 2'-O-methoxyethyl), nucleobase (i.e. 5-methylcytosine) or chimeras, or compositions comprising said compounds and pharmaceutically acceptable diluents or colloidal dispersion systems thereof.

Rothe et al. teach the cDNA sequence encoding Traf-2.

Taylor et al. teach that antisense oligonucleotides 7-30 nucleotides long can be synthesized to inhibit the expression of any protein provided the cDNA sequence is known, and constitute a relatively simple and elegant method of inhibiting such transcripts. Taylor *et al.* also indicate that making and using such oligos are available to those of ordinary skill in the art, that it is common practice to chemically modify the such oligonucleotides to prolong their bioactivity, and also teach that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95% (p. 565).

Baracchini *et al.* teach that antisense oligonucleotides can be used for research purposes, and also teach that preferred antisense oligonucleotides are modified in their sugar, backbone linkage and nucleobase composition (col. 6). Baracchini teaches that such modifications are desirable in antisense oligos because these modifications have desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases. Baracchini et al provide specific embodiments of such modifications at columns 6-8 and in Example 1. These specific examples taught by Baracchini et al include the

presently claimed phosphorothioate linkages, 2'-O-methoxyethyl sugars, 5-methylcytosine and chimeric oligonucleotides. Tables 1-4 show the successful design and use of modified oligonucleotides in cells in culture. Table 1 exemplifies the successful practice of general antisense design taught at columns 8-10. Column 4 teaches various carriers for antisense delivery. Baracchini *et al.* also teaches at column 8 that antisense oligonucleotides are preferably 8 to 30 nucleotides and that it is more preferable to make antisense oligonucleotides that are 12 to 25 nucleotides in length. Baracchini is considered to comprise a detailed blueprint for how to make and use inhibitory antisense oligos to target any known gene.

The teachings of Bennett *et al.* are considered to parallel those of Baracchini *et al.* Bennett *et al.* teaches general antisense targeting guidelines at columns 3-4. Bennett *et al.* also teaches targeting 5'-untranslated regions, start codons, coding regions, and 3'-untranslated regions of a desired target. Bennett teaches, in column 5, for example, that antisense compounds are commonly used as research reagents and diagnostics. Column 5 indicates that antisense oligonucleotides 8-30 nucleotides in length are particularly preferred. Columns 6-7 teach that preferred antisense oligonucleotides contain modified internucleoside linkages including phosphorothioate linkages, among others. Columns 7-8 teach that preferred antisense oligonucleotides comprise modified sugar moieties including 2'-O-methoxyethyl. Bennett *et al.* also teach one of ordinary skill to modify nucleobases in antisense oligonucleotides, including the teaching of 5-methylcytosine (col. 8-9), and also to use chimeric antisense oligonucleotides (col. 9-10). Bennett *et al.* teach that the above modifications are known in the art to provide beneficial attributes to antisense oligonucleotides such as increased hybridization and nuclease protection, for example. Columns 10-24 teach numerous "carriers" for antisense

oligonucleotides. Table 1 teaches the successful targeting of those regions taught in columns 3-4 with chimeric phosphorothioate oligonucleotides having 2'-MOE (a 2'-O-methoxyethyl modification). Thus, Bennett *et al.* is also considered to comprise a detailed blueprint for how to make and use inhibitory antisense oligos to target any known gene.

It would have been obvious to one of ordinary skill in the art to use the cDNA sequence of Rothe et al to generate antisense sequences as taught by Taylor, Baracchini et al. and Bennett for inhibition of Traf-2 expression, and further, it would have been obvious to one of ordinary skill in the art to incorporate modifications as taught by Baracchini *et al.* and Bennett *et al.* into said antisense compounds.

One would have been motivated to create such compounds because both Kaye et al. and Lee et al. expressly teach inhibition of Traf-2 function. Kaye et al. teaches that inhibition of Traf-2 function inhibits an essential event in Epstein-Barr pathogenesis, which would motivate one of ordinary skill to search for other inhibitors such as the instantly claimed antisense sequences. Lee et al. teaches that Traf-2 is a negative regulator of TNF-α induced apoptosis, and directly suggest that inhibition of Traf-2 may successful as part of a larger strategy in treating cancer (see final sentence of discussion).

Furthermore, one of ordinary skill would have been motivated to modify said antisense compounds as taught by Baracchini *et al.* and Bennett *et al.,* because both teach that such modifications increase an antisense compound's cellular uptake, target affinity and resistance to degradation, all of which are valuable modifications for improving biological activity.

Finally, one would have a reasonable expectation of success given that Taylor teaches that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95%, and since Baracchini *et al.* and Bennett *et al.* both teach making modified antisense compounds targeted to distinct regions of a target gene, the steps of which are routine to one of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz, Ph.D. whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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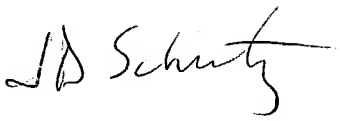

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Art Unit 1635